REMARKS

This is filed in response to the Non Final Office Action dated October 10, 2007, which rejects claims 48-59. Applicants respectfully disagree with the Examiner. However, in an attempt to further prosecution Applicants have amended independent claim 48. Applicants believe that the claim amendments and remarks that follow, place all pending claims in condition for allowance.

Amendments to the Claims:

Claims 1-4, and 6-24 were previously cancelled. Claims 25-47 had been withdrawn from consideration by the Applicants in response to a restriction requirement filed May 6, 2006. Applicants have amended claim 48 to better describe the Applicant's claimed invention and distinguish the claimed invention in light of the cited references. No new subject matter has been added. Support for the amendment of claim 48 can be found in the specification especially in paragraph 60 of the application as filed. Additional support for the subject matter of claim 48 can be found in paragraphs 7, 8, 11, 16, 41, and 82 as well as in examples 5-8 of the application as filed.

Amended claim 48 recites a composition comprising a biocompatible substrate and genetically altered chondrocytes. The genetically altered chondrocytes are modified to express a therapeutic agent at an ectopic site associated with a disorder. Additionally, amended claim 48 requires that *the genetically altered chondrocyte does not perform the function of cartilage tissue and is not used for tissue repair or construction.* The claimed composition is also capable of delivering the expressed therapeutic at a level sufficient to ameliorate the disorder.

None of the cited references disclose the claimed composition either individually or in combination. Amended claim 48 is therefore patentable over the cited references.

Claim Rejections under 35 USC § 102

Claims 48-51 and 54-56 are rejected by the Examiner under 35 U.S.C. 102(b)/(e) as being anticipated by U.S. Patent No. 6,413,511, (Gloriosos et. al., '511 reference). Applicants respectfully disagree.

The instant invention discloses a composition that comprises genetically altered chondrocyte(s) and a biocompatible substrate. The genetically altered chondrocytes are capable of expressing a therapeutic agent in a target region associated with a disorder. Amended claim 48 requires the target region to be an *ectopic site*; in other words, a site which is *atypical of chondrocytes.* Importantly, the *chondrocytes* in the claimed composition *do not perform the function of cartilage tissue (tissue native to chondrocytes) and are not used for tissue repair or construction.* The claimed composition is also capable of delivering the expressed therapeutic agent at a level sufficient to ameliorate the disorder.

The '511 reference does not teach each and every element of amended claim 48 and thus does not anticipate the claimed invention. The '511 reference teaches a method for genetically modifying either chondrocytes or synovial cells and the use of such modified cells in <u>*alleviating pathologies of the joint*</u>. In fact, the main focus of Glorioso et. al. is on the use of genetically altered chondrocytes or compositions containing genetically altered chondrocytes and collagen for the treatment of joint pathologies. Nowhere does the '511 reference disclose delivering compositions comprising genetically altered chondrocytes and a biocompatible substrate to an *ectopic site*, much less compositions wherein the genetically altered chondrocytes *do not perform the function of cartilage tissue and are not used for tissue repair or construction.*

In the current office action (page 3), the Examiner states that that Glorioso discloses delivering genetically altered chondrocytes in a gel matrix to treat arthritis which is an autoimmune disease. Thus according to the Examiner, the claimed invention does not patentably distinguish over the teachings of Glorioso. The Examiner is correct in stating that Glorioso discloses treatments for *arthritic joints,* however, the Examiner has failed to realize that it is the cartilage tissue within the joint that is the site of repair using the genetically modified

chondrocytes. Stated differently, Glorioso is effectively using the modified chondrocyte-gel composition to treat pathology in a *tissue native to the chondrocytes.* As such, cells delivered to treat or repair *native tissue* will have a high propensity of being incorporated within the tissue at the repair site. This is at odds to the claimed invention which clearly requires delivering the genetically altered chondrocytes to an *ectopic site.* Moreover, amended claim 48 explicitly recites that the genetically altered chondrocytes *do not perform the function of cartilage tissue and are not used for tissue repair or construction.*

To anticipate a claim, each and every element of the claim must be found in the prior art reference. As amended claim 48, contains functional limitations that are not present in Glorioso. Namely, claim 48 requires the claimed composition to be capable of delivering the genetically altered chondrocytes to an *ectopic* site. Furthermore, the claimed composition requires the genetically altered chondrocytes *to be incapable of performing the function of cartilage tissue at such a site, nor should the modified chondrocytes be used for tissue repair or construction of new tissue.*

Glorioso only discloses a collagen-chondrocyte composition because such a composition would most likely have a high chance of success when used to treat joint pathologies. Both collagen and chondrocytes are the major components of the cartilage tissue and as mentioned above, the Glorioso reference focuses on treating joint abnormalities due to arthritis.

Furthermore, there would have been no reason for one of ordinary skill, to believe that the modified chondrocytes would be suitable *drug delivery agents* for delivering therapeutics to environments that are *foreign* to these cells. An important reason for the *lack of any disclosure* in Glorioso for using the referenced chondrocyte-gel composition to treat anomalies in regions other than the joints is because, Glorioso had no reason to believe that the referenced composition could be delivered and be used effectively to treat disease in environments *ectopic* to chondrocytes. In fact, without the Applicant's disclosure, one would have thought that using genetically altered chondrocytes to treat disease(s) at a site ectopic to chondrocytes, would not be feasible since there would be no reason to believe that disorders in regions atypical to

chondrocytes may successfully be treated using genetically modified chondrocytes as mere drug delivery agents.

It is only because of the Applicants disclosure that the Examiner, in hindsight, is able to realize the potential benefits of using modified chondrocytes to treat anomalies at ectopic sites without the cells performing the function of cartilage tissue or being used for tissue construction.

Amended claim 48, is therefore patentable in view of the '511 reference. Claims 49-51 and 54-56 depend on patentably distinct amended claim 48, thus incorporating all its limitations. These dependent claims are patentable over Glorioso for at least all the reasons mentioned above for amended claim 48. Additionally, claim 49 is patentably distinct over Glorioso for other independent reasons too. Claim 49 recites the composition of amended claim 48 wherein the composition does not become part of the ectopic target region. As such, Glorioso does not disclose delivering the referenced composition to regions ectopic to the chondrocytes, much less, without the modified chondrocytes not becoming a part of the ectopic region.

Claim Rejections under 35 USC § 103(a):

Claims 52 and 53 are rejected by the Examiner under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,413,511, in view of the article by Bartholomew. Applicants respectfully disagree.

The Examiner cites the article by Bartholomew to teach modified chondrocytes capable of secreting erythropoietin (EPO), or the EPO mimetibody. According to the Examiner, Bartholomew in combination with Glorioso render the teachings of claims 52 and 53 obvious.

As mentioned above in response to the rejections in the 102 section, Glorioso does not teach or suggest the claimed composition. Glorioso focuses on treating pathologies of the joint using *genetically modified chondrocytes.* As such, the modified chondrocytes in Glorioso's composition are being delivered to tissue native to the chondrocytes (namely, cartilage) and would therefore be able to perform the function of cartilage tissue. Moreover, the modified

chondrocytes are being used for tissue construction, namely, the construction of *new cartilage tissue.*

Bartholomew, evaluates the usefulness of genetically altered human or baboon *mesenchymal stem cells* (bMSC) in gene therapy. Specifically, Bartholomew discloses the use of immunoisolatory devices (IID's) for delivering modified bMSC's expressing human EPO to baboons, and the results from in-vitro and in-vivo studies aimed at determining the level of EPO expressed by these cells. There is no teaching or suggestion in Bartholomew of using a biocompatible substrate in place of the IID's to deliver genetically modified cells nor is there any teaching of genetically altered cells capable of expressing an EPO mimetibody. Moreover, Bartholomew fails to disclose the use of genetically altered *chondrocytes* for expressing EPO or its mimetibody, much less the ability of the modified chondrocytes to express the therapeutic when delivered at an *ectopic* site.

Thus, Bartholomew does not teach the elements of claim 48 and it certainly does not teach the additional element of claims 52 and 53, namely, the expression of an erythropoietin or EPO mimetibody using genetically altered chondrocytes. Furthermore, Bartholomew does not remedy the deficiencies of the Glorioso reference.

Moreover, Applicants respectfully note that it is the Examiner who has the burden to show why one of ordinary skill in the art would consider *substituting* the *mesenchymal stem cells* disclosed in Bartholomew *with chondrocytes* for expressing EPO or its mimetibody. Also, it should be noted that the Examiner has failed to show why one of ordinary skill would replace the referenced immunoisolatory devices with a biocompatible substrate, since Bartholomew fails to suggest combining the mesenchymal cells with a biocompatible matrix. In accordance with MPEP § 2141(II)(B), "[t]he references must be considered as a whole and *must suggest the desirability* and thus the obviousness of making the combination" (emphasis added).

The two references in combination have failed to render obvious the claimed invention. Rather, it is the Examiner who has determined that it would be *obvious to combine* the teachings of Bartholomew with Glorioso to build the claimed composition; a composition using modified

chondrocytes to express erythropoietin or its mimetibody when delivered to an ectopic target site *without the chondrocytes performing the function of cartilage tissue or participating in tissue repair or construction.*

Thus, neither references alone nor in combination teach all the elements of independent claim 48 or claims 52 and 53 that depend therefrom.

Claims 57-59 are rejected by the Examiner under 35 U.S.C. 103(a) as being unpatentable over Glorioso, in view of the article by Okada (Biol. Pharm. Bull. 1997, Vol. 20, No. 3, p 255-258). Applicants respectfully disagree.

The Okada reference is cited to teach the encapsulation of cells within an agarose matrix. Specifically Okada discloses encapsulating SK2 hybridoma cells secreting anti-hIL6 monoclonal antibodies to suppress IgG1 plasmocytosis in transgenic mice. Okada certainly does not teach all the elements of amended claim 48 and this reference does not remedy the teachings of Glorioso either. Claims 57-59 ultimately depend on amended claim 48 which is patentably distinct over the combination of Okada and Glorioso. The dependent claims incorporate the limitations of the base claim and are thus patentable for at least the same reasons mentioned for claim 48.

Conclusion

Applicants submit that claims 48-59 are allowable, and allowance thereof is respectfully requested. The Examiner is encouraged to telephone the undersigned attorney for Applicants if such communication is deemed necessary to expedite prosecution of this application.

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Respectfully submitted,

By_____

George Xixis
Registration No.: 38,664
NUTTER McCLENNEN & FISH LLP
World Trade Center West
155 Seaport Boulevard
Boston, Massachusetts 02210-2604
(617) 439-3746
Fax: (617) 310-9746
Attorney for Applicant

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